SYNTHESIS OF 4-AMINO-4-(*S*)-DIHYDROSPECTINOMYCIN

Sir:

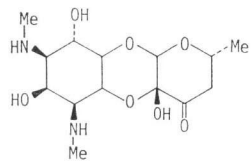
Over the past decade, extensive studies have been done in the chemical modification of spectinomycin (**1**), in an effort to improve its biological activity.[1] Recent studies in this area have also resulted in two total syntheses[2,3] of this unique structure and the establishment of the stereochemical identity[4] of spectinoic acid, a rearrangement product of spectinomycin[5].

A recent patent[6] has disclosed the preparation of 4-amino-4-(*R*)-dihydrospectinomycin from the parent antibiotic. This product has shown unexpectedly improved biological activity against a variety of microorganisms. We wish to report our concurrent studies along the same lines and the synthesis of 4-amino-4-(*S*)-dihydrospectinomycin (**2**) from 4-(*S*)-dihydrospectinomycin (Scheme 1).

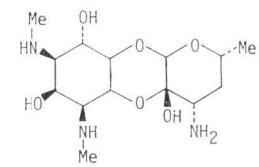
Treatment of the known N,N′-dibenzyloxycarbonyl dihydrospectinomycin[7] (**3**) with methanesulfonylchloride in pyridine (1.3 equiv. 0°C, 18 hours) gave the corresponding methanesulfonate derivative **4** as a chromatographically homogeneous amorphous solid (79%); $[\alpha]_D \pm$ 2.6° ($CHCl_3$); *m/z* 584.236 ($M^+ - CH_3SO_3H$). Treatment of **4** with excess silver carbonate in 1:1 aq. acetone (reflux, 18 hours) gave the known[7,8] N,N′-dibenzyloxycarbonyl-4-(*R*)-dihydrospectinomycin (47%, identical with authentic material), and N,N′-dibenzyloxycarbonyl-actinamine as a byproduct.

Treatment of **4** with sodium azide (15 equiv.) in 1.5% aq. trifluoroethanol (reflux, 4 hours), gave after chromatographic separation, a product which was characterized as N,N′-dibenzyloxycarbonyl-4-azido-4-(*S*)-dihydrospectinomycin (**5**) (amorphous solid, 68% based on recovered starting material, 30% isolated) $[\alpha]_D$+20.1° ($CHCl_3$) (Scheme 2). Catalytic hydrogenation (10% Pd/C, H_2, EtOH, dil. HCl) gave 4-amino-4-(*S*)-dihydrospectinomycin (**2**) as a colorless solid (92%), mp 198~200°C (dec.); $[\alpha]_D$+11.4° (H_2O); *m/z* 334 (M^++H); 316 ($M^+ - H_2O$) *etc.* ^{1}H n.m.r data at 400 MHz (D_2O): p.p.m 1.35 (d, 3H, C-2 Me, J=6.2 Hz), 1.77 (dd, 1H, H_{3a_x}, $J_{3a_x,3eq}$= 12.8 Hz; $J_{3a_x,4a_x} \simeq J_{3a_x,2a_x}$=12.7 Hz), 2.06 (m, 1H, H_{3eq} $J_{3eq,4a_x}$=4.9 Hz; $J_{3eq,2a_x}$=1.7 Hz), 2.88 (s, 6H, N-Me), 3.32 (dd, 1H, H_6, $J_{6,5a}$=10.1 Hz; $J_{6,7}$=2.9 Hz), 3.61 (dd, 1H, H_8, $J_{8,9}$=11.0 Hz, $J_{8,7}$=2.8 Hz), 3.71 (dd, 1H, H_4), 3.95 (m, 1H, H-2), 4.03 (dd, 1H, H-5_a, $J_{5a,9a}$=10.1 Hz), 4.11 (dd, 1H, H-9a, $J_{9a,9}$=10 Hz), 4.37 (dd, 1H, H-9), 4.79 (dd, 1H, H-7), 4.96 (s, 1H, H-10_a). The above assignments were confirmed by decoupling experiments and it was conclusively estab-

Scheme 1.

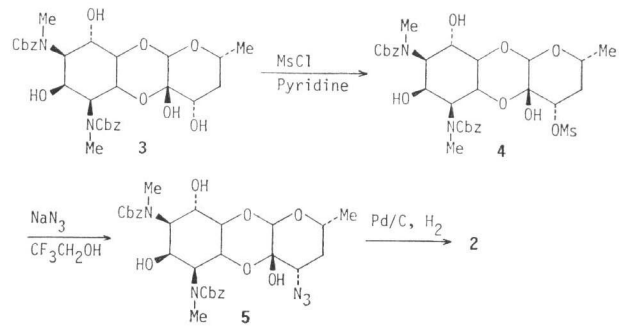


Spectinomycin, **1**

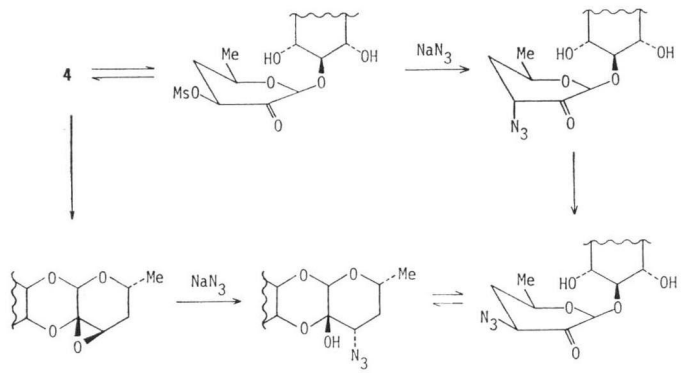


4-Amino-4-(*S*)-dihydrospectinomycin, **2**

Scheme 2.



Scheme 3.



lished that the 4-amino group had an equatorial disposition, contrary to expectations based on an S_N2 type displacement of the mesylate and the solvolysis described above. Although the physical constants of the 4-(*S*)- and 4-(*R*)[6] amino derivatives are quite similar, their n.m.r. spectra and chromatographic properties were different.*

Compound **5** is therefore formed from **4** by a mechanism that promotes *retention* of configuration at C-4. We suggest two possibilities to account for this process as illustrated in Scheme 3. The mesylate **4** could in fact react as the α-keto mesylate which would be much more reactive[9] as compared to the bicyclic form **4**, and it would also be sterically favorable to an S_N2 type displacement reaction.** The azido derivative thus produced can now undergo epimerization and subsequent diastereoselective intramolecular acetal formation as expected of such a derivative[3,10] to give the observed product **5**. Alternatively the trans disposition of the tertiary hydroxyl group and the mesylate function could initially lead to epoxide formation, which could undergo regio- and stereoselective opening with azide ion. Other possibilities as proposed for the reaction of α-keto triflates[11] could also be considered but may not be operative in this case.

To the best of our knowledge, the C-4 position in the dihydrospectinomycins has so far remained unexploited.[6] The mechanistic outcome of the displacement of the novel 4-(*S*)-mesylate derivative of dihydrospectinomycin may have relevance in future work aimed at introducing other functionality at that position. It should be noted however that 4-(*S*)-derivatives containing leaving groups such as in **4** are prone to stereoelectronically-controlled rearrangements, involving the antiperiplanar C-4a–C-10a bond[12]* similar to other GROB-type fragmentations.[13] Unlike the 4-amino-4-(*R*)-dihydrospectinomycin (spectinomyclamine)[6] the synthetic 4-(*S*)-analog was found to be devoid of antibacterial activity.

Acknowledgements

We thank the National Science and Engineering Council of Canada and le Ministère de l'éducation du Québec for financial assistance. We also thank Dr. H. BEIERBECK of this department for recording the 400 MHz spectra and Dr. W. ROSENBROOK, Abbott Laboratories, North Chicago, Ill. for antibacterial assays and mass spectrometric data.

STEPHEN HANESSIAN
RENE ROY
MICHEL THERIEN**
DANIEL DELORME**

Department of Chemistry
University of Montreal
C.P. 6210, Succ. A
Montreal, Quebec
Canada H3C 3V1

(Received December 13, 1980)

* We thank Dr. R. MAIER, K. THOMAE for sending us a 250 MHz ^1H n.m.r spectrum of 4-amino-4-(*R*)-dihydrospectinomycin.

** Models show that backside approach at C-4 is not favored in the conformationally rigid tricyclic structure **4**.

* There are two major byproducts in the azide displacement reaction which could arise from such a rearrangement. These are under study.

** Summer undergraduate research participant.

References

1) ROSENBROOK, W., Jr.: Chemistry of spectinomycin. Jpn. J. Antibiotics 32 Suppl.: S-211~S-227, 1979; and references cited therein.
MARING, C. J. & D. R. WHITE: Spectinomycin chemistry. II. The synthesis of 6'-substituted spectinomycin analogs. Tetrahedron Lett. 21: 4065~4068, 1980
FOLEY, L.; J. T. S. LIN & M. WEIGELE: Spectinomycin chemistry. III. 9-Epi-4-(*R*)-dihydrospectinomycin and 9-epi-spectinomycin. J. Antibiotics 31: 985~990, 1978

2) WHITE, D. R.; R. D. BIRKENMEYER, R. C. THOMAS, S. A. MIZSAK & V. H. WILEY: The stereospecific synthesis of spectinomycin. Tetrahedron Lett. 1979: 2737~2740, 1979

3) HANESSIAN, S. & R. ROY; Synthesis of (+)-spectinomycin. J. Am. Chem. Soc. 101: 5839~5841, 1979
HANESSIAN, S. & R. ROY: Studies directed toward the total synthesis of antibiotics: (+)-spectinomycin. Jpn. J. Antibiotics 32 Suppl.: S-73~S-90, 1979

4) HANESSIAN, S. & R. ROY: A stereocontrolled rearrangement of spectinomycin. The stereochemical identity of spectinoic acid. Tetrahedron Lett., in press.

5) WILEY, P. F.; A. D. ARGOUDELIS & H. HOEKSEMA: The chemistry of actinospectacin. IV. The determination of the structure of actinospectacin. J. Am. Chem. Soc. 85: 2652~2659, 1963

6) MAIER, R.; F. WOLTUN, W. REUTER, B. WELTZEL, H. GOETH & U. LECHNER: 4-Spectinomycylamin und sein physiologisch verträgliche Salze, Verfahren zur Herstellung und diese stoffe enthaltende Arzneimittel. Europ. Pat. 78,101,542, 1979

7) KNIGHT, J. C. & H. HOEKSEMA: Reduction products of spectinomycin. J. Antibiotics 28: 136~142, 1975

8) ROSENBROOK, W., Jr.; R. E. CARNEY, R. S. EGAN, R. S. STANASZEK, M. CIROVIC, T. NISHINAGA, K. MOCHIDA & Y. MORI: Spectinomycin modification. II. 7-Epi-spectinomycin. J. Antibiotics 28: 960~964, 1975

9) SIMOND, D. S., Jr.; M. PONS & D. F. JOHNSON: α-Keto mesylate: A reactive thiol-specific functional group. J. Org. Chem. 45: 3084~3088, 1980

10) FOLEY, L. & M. WEIGELE: Spectinomycin chemistry. 1. Characterization of a 5a,9a-epi-4-(*R*)-dihydrospectinomycin derivative. J. Org. Chem. 43: 4355~4359, 1978

11) CREARY, X. & A. J. ROLLIN: Reactions of bicyclic α-keto triflates with bases and nucleophiles. J. Org. Chem. 44: 1798~1806, 1979

12) HANESSIAN, S. & R. ROY: unpublished observations, see also ref. 4

13) GROB, C. A.: Mechanism and stereochemistry of heterolytic fragmentations. Angew. Chem., Internat. Edit. 8: 535~546, 1969
GROB, C. A. & P. W. SEHEISS: Heterolytic fragmentation. A class of organic reactions. Angew. Chem., Internat. Edit. 6: 1~15, 1967